Cysteine derivatives as inhibitors for carboxypeptidase A: synthesis and structure-activity relationships.

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A series of cysteine (Cys) derivatives having an alkyl or arylalkyl moiety on the alpha-amino group of the amino acid have been synthesized as a novel type of inhibitor for carboxypeptidase A. These compounds are readily prepared starting with Cys in an optically active form. The structure-activity relationship study revealed that the inhibitors prepared from D-Cys are much more potent than the corresponding inhibitors obtained from L-Cys, and the most potent inhibitor in the series, (S)-1j with a K(i) value of 55 +/- 4 nM, is obtained by introducing a phenethyl moiety on the amino group of D-Cys. In comparison, the most active inhibitor in the series of 2-substituted 3-mercaptopropanoic acid is found to be 20, in which the phenyl ring is linked to the mercaptocarboxylic acid at the alpha-position with a methylene unit. A proposal that accounts for the different structural requirement for the maximum activity between the two series of inhibitors is provided.

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ELSEVIER SCIENCE FULL-TEXT ARTICLE

N-(Hydroxyaminocarbonyl)phenylalanine: a novel class of inhibitor for carboxypeptidase A.

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N-(Hydroxyaminocarbonyl)phenylalanine (1) was designed rationally as a new type of inhibitor for carboxypeptidase A (CPA). The designed inhibitor was readily prepared from phenylalnine benzyl ester in two steps and evaluated to find that rac-1 inhibits CPA in a competitive fashion with the Ki value of 2.09 microM. Surprisingly, inhibitor 1 having the D-configuration is more potent (Ki = 1.54 microM) than its antipode by about 3-fold. A possible explanation for the stereochemistry observed in the inhibition of CPA with 1 is presented.

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